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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/963,698	09/26/2001	Francis Barany	19603/3355 (CRF D-1595E)	2018
7590 Michael L. Goldman NIXON PEABODY LLP Clinton Square P.O. Box 31051 Rochester, NY 14603			EXAMINER LIU, SUE XU	
			ART UNIT 1639	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/963,698	Applicant(s) BARANY ET AL.	
	Examiner SUE LIU	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 89-112 and 148-153 is/are pending in the application.
- 4a) Of the above claim(s) 98-108 and 110 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 89-97, 109, 111, 112 and 148-153 is/are rejected.
- 7) ☒ Claim(s) 89 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/08/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/8/07 has been entered.

Claim Status

2. Claims 1-88 and 113-147 have been canceled.

Claim 149-153 have been added as filed on 3/14/08.

Claims 89-112 and 148-153 are currently pending

Claims 98-108 and 110 have been withdrawn;

Claims 89-97, 109, 111, 112 and 148-153 are being examined in this application

Election/Restrictions

3. Claims 98-108 (dependent on claim 99), 110 are withdrawn from further consideration as acknowledged in the previous office actions.

Priority

4. This application is a divisional of application 08/794,851 (filed 2/04/1997; now US 6,852,487), which claims priority to US provisional application 60/011,359 (filed on 2/9/1996).

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No 60/011,359, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The instant claims have been amended to recite new features including "selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides..." and "to prevent cross-reactivity", which do not appear to have support in the provisional application.

Thus, the instant application does not obtain the benefit of the early filing date of the provisional application.

Information Disclosure Statement

5. The information disclosure statement filed on 11/08/07 has been considered. See attached PTO 1449 form.
6. The information disclosure statement filed 11/29/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the following references are missing date information as listed in the filed IDS: "BIOCOMPARE". It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

7. Applicant's submission of a substituted Abstract is acknowledged and entered.

Claim Objection(s) / Rejection(s) Withdrawn

8. Upon further consideration, the following claim rejections as set forth in the previous office action are withdrawn:
 - A.) Claims 89, 93 and 148 are rejected under 35 U.S.C. 102(b) as being anticipated by Lipshutz et al (BioTechniques, Vol 19, No. 3, 1995, pages 442-447).

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B.) Claims 89 and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor et al (Nature, vol. 364, August 1993, pages 555-556).

C.) Claims 89-93, 96-97, 109, 111 and 148 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,700,637 (SOUTHERN).

D.) Claims 89, 91, 93, 96, 111 and 148 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,837,832 (Chee et al).

E.) Claims 89-97, 109, 111, 112 and 148 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,510,270 (Fodor et al).

F.) Claims 89-94, 96-97, 109, 111, 112 and 148 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,527,681 (HOLMES et al).

G.) Claims 89-97, 109, 111, 112 and 148 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New Claim Objection(s) / Rejection(s)

Claim Objections

9. Claim 89 is objected to because of the following informalities: The definite article “the” is missing in front of the term “multimer” (after the term “attaching”) in line 13. Appropriate correction is required.

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Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

11. Claims 89-97, 109, 111, 112, 148-151 and 153 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite a method of forming arrays of oligonucleotides on a solid support comprising:

providing a solid support having an array of positions each suitable for attachment of an oligonucleotide;

attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and

forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising:

activating selected array positions for attachment of multimer nucleotides;

selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in the multimers are complementary to each other and the multimers would not result in self-pairing or hairpin formulation; and

attaching multimer nucleotides at the activated array positions, wherein the multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides and so that each of the capture oligonucleotides have substantial sequence differences to prevent cross-reactivity, wherein the multimer is formed from multiple nucleotides linked together.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

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Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.S.C. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions and includes chemical inventions. The fact that the patent is directed to method entailing use of compounds, rather than to compounds per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to consider the decision of the Court of Appeals for the Federal Circuit, which holds that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

The instant claims are drawn to a genus of methods of making various nucleic acid arrays with various nucleic acid probes. Claim 89 is drawn to a genus of "multimer nucleotides" that can use to form a genus of "capture oligonucleotides" that have various sequences. Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of oligonucleotides. In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genus of oligonucleotides.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties,

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functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (see MPEP 2163 II).

In this case, the instant application only provides one example of using unique tetramers (as listed in Table 1) to generate oligonucleotides attached to nucleic arrays.

The Court of Appeals for the Federal Circuit, our reviewing court, has addressed the issue of what constitutes adequate written description for a claim drawn to a nucleic acid. In Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1602 (Fed. Cir. 2002), the court adopted a portion of the Guidelines proffered by the United States Patent and Trademark Office (USPTO). The court stated that:

The written description requirement can be met by “showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics.

Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613 (citations omitted).

The court also addressed the issue of what constitutes adequate written description of a claim to a broad genus of sequences. In The Regents of The University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1998), the court determined that the disclosure of rat cDNA did not provide adequate written description support for claims drawn to mammalian and vertebrate DNA. Eli Lilly, 119 F.3d at 1567-68, 43 USPQ2d at 1405. The court stated:

In claims to genetic material, however, a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA,” without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

In Enzo-Biochem, the court refined the approach advanced by Eli Lilly, adopting an example offered in the USPTO guidelines having facts that contrasted with those of Eli Lilly, wherein the written description requirement would be met. Thus, adequate written description may be present for a genus of nucleic acids based on their hybridization properties, “if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar.” Enzo Biochem, 296 F.3d at 1327, 63 USPQ2d at 1615.

Here, Applicants fail to claim probes that hybridize under “stringent” conditions. Thus, the current claims encompass a myriad of probes that are not “structurally similar.” This would include virtually an infinite number of possibilities. This also would lead to a target that could potentially bind to numerous “low affinity” probes.

Therefore, applicants are not in possession of the claimed genus of oligonucleotide probes and/or “multimer” building blocks. Applicant’s claimed scope represents only an invitation to experiment regarding possible oligonucleotides that can be use to generated the claimed genus of arrays.

Second paragraph of 35 U.S.C. 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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13. Claims 89-97, 109, 111, 112 and 148-153 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 89 recites “selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in the multimers are complementary to each other...” The instant claim 152 recites “the multimers” are “tetramers” as set forth in “Table 1”. However, at least some tetramers listed in Table 1 do not differ “by at least 2 nucleotide”. For example, the listed number 1 and 2 tetramer in Table 1 has sequences, TGTC and TCTG respectively, which two sequences would not be considered to be differed by “at least 2 nucleotides” (the last two nucleotides of number 1 is the same as the first two nucleotides of number 2, and the first two nucleotides of number 1 is the same as the last two of number 2). In addition, all four nucleotides of number 1 is the same as the four nucleotides of number 2. Further, the last two nucleotides of number 16 (in Table 1) is “complementary to the first two nucleotides of number 8. As discussed above, recitation of the instant claim 89 seems to be in conflict with the recitation of claim 152. It is not clear what “multimer” and “dimer” are encompassed by the said claim limitation.

Claim 109 recites the limitation "the surface". There is insufficient antecedent basis for this limitation in the claim. Claim 89 recites “surfaces” in plural, but Claim 109 recites a singular “surface”. It is not clear to which “surface” Claim 109 is referring.

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Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(Note: the instant claim numbers are in bold font.)

Fodor and Others

16. Claims **89-97, 109, 111, 112** and **148-153** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Fodor** et al (US Patent 5,510,270; 4/23/1996; earlier filing date 1992; cited previously), in view of **Brennan** et al (US 5,474,796; 12/12/1995) and **Froehler** et al (US 5,594,121; 1/14/1997; filing date 6/7/1995; cited in IDS).

The instant claims recite a method of forming arrays of oligonucleotides on a solid support comprising:

providing a solid support having an array of positions each suitable for attachment of an oligonucleotide;

attaching linkers to the solid support surfaces, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and

forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising:

activating selected array positions for attachment of multimer nucleotides;

selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in the multimers are complementary to each other and the multimers would not result in self-pairing or hairpin formulation; and

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attaching multimer nucleotides at the activated array positions, wherein the multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides and so that each of the capture oligonucleotides have substantial sequence differences to prevent cross-reactivity, wherein the multimer is formed from multiple nucleotides linked together.

Fodor et al, throughout the patent, teach a method for synthesizing and screening oligonucleotides on a solid support (e.g. Abstract), which the solid support read the first step of **clm 89**. The method provides for the irradiation of a first predefined region of a substrate comprising immobilized nucleotides on its surface, without irradiation of a second predefined region of the substrate. The irradiation step removes a protecting group from the immobilized nucleotides. The substrate is contacted with a first nucleotide to couple the nucleotide to the immobilized nucleotides in the first predefined region without coupling in the second predefined region. At least a part of the first predefined region and at least a part of the second predefined region are subjected to further irradiation. The substrate is contacted with a second nucleotide, which couples to the immobilized nucleotides in at least part of the first and at least part of the second predefined regions. By repeating these steps, an array of diverse oligonucleotides is formed on the substrate (refers to the instant claimed method) (i.e., see abstract). The reference teachings read on the activating and attaching steps of **clm 89**. The reference also teaches using linker on the substrate for attaching nucleic acid probes onto the substrate (e.g. col.3, lines 1+), which read on the attaching linker step of **clm 89**.

Fodor et al use a mask to illuminate(or irradiate) selected regions of the substrate and uses photolithographic technique in synthesis of polymer arrays. Fodor et al teach that a square area is divided into square boxes, and the first reactions are carried out in the vertical columns

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and the process is repeated in the horizontal direction for the second unit of dimmer (i.e., see columns 18-19). Fodor et al teach that one mask can be used in all eight steps if it is suitably rotated and translated. For example, a mask with a single transparent region could be sequentially used to expose each of the vertical columns, translated 90° and then sequentially used to allow exposure of the horizontal rows. Fodor et al teach that by controlling the locations of the substrate exposed to light and the reagents exposed to the substrate following exposure the locations of each sequence will be known (i.e., see column 9). The reference's teachings read on the method steps of **clm 90**.

Fodor et al teach that the substrate surface is composed of inorganic glass (i.e., see column 11), which reads on **clms 91-92**. Fodor et al teach that the substrate is conventional microscope slide or coverslip (i.e., see column 16) (refers to instant **clm 92**).

The reference also teaches the substrate having different positions and attached nucleic acid probes (e.g. Figure 10; cols.9+; col.15, lines 28+), which read on the different sequence on different positions of **clm 93**.

Fodor et al teach the solid support is substantially flat and may have wells, raised regions, etched trenches, or the like (i.e., see column 7, under substrate or in column 11), which reads on **clm 94**. The reference also teaches the substrate is a plate (e.g. col.11, lines 5+) and microtiter plate (e.g. col.2, lines 54+), which would render **clm 95** obvious because using microtiter plate as support for nucleic acid microarray is routine and known in the art as taught by Fodor et al.

The reference also teach functionalizing the substrate such as using silanized substrate (e.g. col.22, lines 54+), which reads on **clm 96**. Fodor et al teach that the surface of the substrate

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contains reactive groups which can be carboxyl, amino, hydroxyl (i.e., see column 11), which reads on **clm 97**.

Fodor et al teach that the any conceivable substrate may be employed in the invention. Fodor et al teach that the substrate is polymerized with gels or polymers such as (poly)tetrafluoroethylene, (poly)vinylidenedifluoride, polystyrene, polycarbonate (e.g. see column 11) as well as silanized substrate (e.g. col.22), which reads on **clm 109**.

The reference also teaches making polymers (including nucleotide probes) with different length such as greater than 16 nucleotides (e.g. cols.9-10, bridging), which reads on **clm 148**.

Fodor et al do not explicitly teach attaching “multimer nucleotides” to each activated position at each cycle of synthesis using “multimers” that are different “from each other by at least 2 nucleotides...” as recited in **clm 89**. The recitation “selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in the multimers are complementary to each other...” is unclear and can be interpreted variously as discussed supra (see the Claim Rejection under 35 USC 112 2nd paragraph). The reference also does not explicitly teach a difference of “at least 25% of its nucleotides” and at least 6 nucleotides as recited in **clms 111** and **153**, barrier oligonucleotides recited in **clm 112**, using the various multimers as recited in **clms 149-152**.

However, Fodor et al, throughout the patent, teach the above discussed methods of making DNA microarray are applicable for making any DNA microarray with any nucleic acid sequence of desire or interest (e.g. col.10)

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In addition, **Brennan** et al, throughout the patent, teach making and using various arrays (comprising various “sectors” (i.e. sub-arrays)) with various probes. The reference also teaches using arrays with 3-mers and 10-mers attached thereto such that the “total array presents every possible permutation of the 10-mer oligonucleotides” (col. 9, lines 48+). That is the taught array comprises all possible 3-mers or 10-mers that can be generated, and would provide probes that “differs from its adjacent capture oligonucleotides by at least 25%”, or by at least 6 nucleotides because the all possible permutations of 10-mer oligonucleotides would encompass all different sequences. The all possible permutations would also encompass multimers different by at least 2 nucleotides.

Further, **Froehler** et al, throughout the patent, teach generating various nucleic acid probes by linking multimers together (e.g. col.6, lines 64+; col.10, lines 1+). The reference also teaches multimer with various lengths including “tetramer” (e.g. col.10, lines 1+). The reference also teaches the advantage of using “multimer” or oligomers to synthesize longer oligomers as the multimer intermediates offer valuable synthons for convenient synthesis of longer oligomers (e.g. col.10, lines 1+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to link “multimers” (or oligomers) with various lengths (including “tetramers”) and desired sequences together to form longer oligomers as nucleic acid probes on nucleic acid arrays.

A person of ordinary skill in the art would have been motivated at the time of the invention to using oligomers with at least 2 nucleotides difference as building blocks for generating longer oligomers on an array, because Brennan et al teach making probes with

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different sequences (or all possible permutations) are routine and known in the art, Fodor also teaches making array with desired sequences are routine and known in the art, Froehler teaches linking various oligomers together to form longer oligomers are routine and known in the art. Because all of the cited references teach methods making DNA microarray (including making probes) or making various DNA probes with various desired sequences, it would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 2 nucleotides) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce cross-reactivity among the attached probes (and therefore improve accuracy of the detections). It would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 25% of its nucleotides or at least 6 nucleotides) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce the formation of hairpins in the probes themselves.

A person of ordinary skill in the art would have been motivated at the time of the invention to generate “barrier oligonucleotides” adjacent to the “capture oligonucleotides”, because all of the cited references teach oligonucleotides with various lengths and sequences can be generated using known and routine methods. In addition, Fodor also teaches attaching specific oligonucleotides at specific position on an array is also routine and known in the art. Thus, It would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with shorter nucleotide lengths) to achieve the predictable result of

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making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to improve the cross-reactivity of the attached probes.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of making nucleic acid arrays and generate nucleic acid probes using various building blocks such as multimers/oligomers with different sequences.

Holmes and Others

17. Claims **89-94, 96-97, 109, 111, 112** and **148-153** are rejected under 35 U.S.C. 103(a) as being unpatentable over **HOLMES** et al (US Patent 5,527,681; 6/18/1996; filed 11/5/1992; cited previously), in view of **Brennan** et al (US 5,474,796; 12/12/1995) and **Froehler** et al (US 5,594,121; 1/14/1997; filing date 6/7/1995; cited in IDS).

Holmes et al teach a synthetic strategy for the creation of large scale chemical diversity using solid phase chemistry, photo labile protecting groups and photolithography achieve light directed spatially addressable parallel chemical synthesis of an array of polymers (i.e., see abstract). Holmes teaches that the preferred embodiment provides for the synthesis of an array of polymers in which individual monomers in a lead polymer are systematically substituted with monomers from one or more basis sets of monomers. The reference teaches that the substrate is flat and it may have synthesis regions separated by structures, and the surface may have wells, raised regions, or etched trenches (i.e., see column 5). The reference teaches that the substrate has linker molecules, which are optionally protected with photo removable protecting groups. The reference teaches that the mask is used and rotated for the following coupling steps. The

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reference claims and specification disclosure are drawn to a method of synthesizing an array of oligonucleotides on a surface of a substrate clearly anticipates the claimed invention.

Holmes et al teach the substrate with surface, and optional Linker molecules are provided on the surface (i.e., see column 7).

The reference teaches thus formed oligonucleotide array will have variety of uses including, screening large number of polymers for biological activity by exposing the array to receptors. The receptor chosen can be a nucleic acid sequence (i.e., see column 4, definition of receptor). And the reference claim recites that the oligonucleotide array is contacted with a receptor (nucleic acid) to identify an oligonucleotide complementary to said receptor (refers to the oligonucleotide target sequence). NOTE In the claimed method of forming array of oligonucleotides, the limitation ‘the capture oligonucleotides on the array hybridize with complementary oligonucleotide target sequences under uniform conditions’ is considered as the intended use of thus formed array, not the method step. Thus the reference clearly anticipates the claimed invention.

The reference teaches generating probes with various lengths, for examples, between 2-20 nucleotides (cols. 9. lines 20+), which reads on the length as recited in the instant claim 148.

Holmes et al do not explicitly teach attaching “multimer nucleotides” to each activated position at each cycle of synthesis using “multimers” that are different “from each other by at least 2 nucleotides...” as recited in **clm 89**. The recitation “selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in the multimers are complementary to each other...” is unclear and can be interpreted variously as discussed supra (see the Claim Rejection under 35 USC 112 2nd paragraph). The reference

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also does not explicitly teach a difference of “at least 25% of its nucleotides” and at least 6 nucleotides as recited in **clms 111** and **153**, barrier oligonucleotides recited in **clm 112**, using the various multimers as recited in **clms 149-152**.

However, Holmers et al, throughout the patent, teach the above discussed methods of making DNA microarray are applicable for making any DNA microarray with any nucleic acid sequence of desire or interest (e.g. Figures 1-2) .

In addition, **Brennan** et al, throughout the patent, teach making and using various arrays (comprising various “sectors” (i.e. sub-arrays)) with various probes. The reference also teaches using arrays with 3-mers and 10-mers attached thereto such that the “total array presents every possible permutation of the 10-mer oligonucleotides” (col. 9, lines 48+). That is the taught array comprises all possible 3-mers or 10-mers that can be generated, and would provide probes that “differs from its adjacent capture oligonucleotides by at least 25%”, or by at least 6 nucleotides because the all possible permutations of 10-mer oligonucleotides would encompass all different sequences. The all possible permutations would also encompass multimers different by at least 2 nucleotides.

Further, **Froehler** et al, throughout the patent, teach generating various nucleic acid probes by linking multimers together (e.g. col.6, lines 64+; col.10, lines 1+). The reference also teaches multimer with various lengths including “tetramer” (e.g. col.10, lines 1+). The reference also teaches the advantage of using “multimer” or oligomers to synthesize longer oligomers as the multimer intermediates offer valuable synthons for convenient synthesis of longer oligomers (e.g. col.10, lines 1+).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to link “multimers” (or oligomers) with various lengths (including “tetramers”) and desired sequences together to form longer oligomers as nucleic acid probes on nucleic acid arrays.

A person of ordinary skill in the art would have been motivated at the time of the invention to using oligomers with at least 2 nucleotides difference as building blocks for generating longer oligomers on an array, because Brennan et al teach making probes with different sequences (or all possible permutations) are routine and known in the art, Holmes also teaches making array with desired sequences are routine and known in the art, Froehler teaches linking various oligomers together to form longer oligomers are routine and known in the art. Because all of the cited references teach methods making DNA microarray (including making probes) or making various DNA probes with various desired sequences, it would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 2 nucleotides) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce cross-reactivity among the attached probes (and therefore improve accuracy of the detections). It would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 25% of its nucleotides or at least 6 nucleotides) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce the formation of hairpins in the probes themselves.

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A person of ordinary skill in the art would have been motivated at the time of the invention to generate “barrier oligonucleotides” adjacent to the “capture oligonucleotides”, because all of the cited references teach oligonucleotides with various lengths and sequences can be generated using known and routine methods. In addition, Holmes also teaches attaching specific oligonucleotides at specific position on an array is also routine and known in the art. Thus, It would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with shorter nucleotide lengths) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to improve the cross-reactivity of the attached probes.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of making nucleic acid arrays and generate nucleic acid probes using various building blocks such as multimers/oligomers with different sequences.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

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ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 89 and 149-151 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 10/257,158 (PGPUB 20050142543; hereinafter referred to as ‘158 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention of the ‘158 application reads on the instant claimed invention.

The ‘158 application claims a method of making a substrate by attaching various nucleic acid probes through linking “multimers” together on the substrate (claim 1), which the substrate read on an array, and the capture probes read on the capture probes of the instant claim 89.

The ‘158 application also teaches linking the tetramers together on various positions on the solid support (see claims 1 and 2), which read on the cycles of attaching multimers to the solid support of the instant claim 89.

The ‘158 application also claims using linkers and the multimers are “tetramers” (claim 1), which read on the tetramer of the instant claims 149-151.

Thus, the claimed invention of the ‘158 application reads on or is obvious over the instant claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. It is noted that a “Notice of Allowance” for the ‘158 application has been mailed on 6/18/08. In case of the actual issuance of the ‘158 application as a

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US Patent, the instant ODP rejection will be not be a “provisional” rejection over the granted patent.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Patent Examiner, Art Unit 1639
7/3/08